ABSTRACT

"Clinical Protocol for Modification of Oncogene and Tumor Suppressor Gene Expression in Non-Small Cell Lung Cancer (NSCLC)", Jack A. Roth, M.D., Study Chairman

The objective of this protocol is to evaluate the toxicity and possible therapeutic efficacy of the intralesional administration of retroviral constructs containing antisense (AS) K-*ras* (for tumors with mutated K-*ras*) and wildtype *p53* (wt*p53*) (for tumors with mutated or deleted *p53*) into residual endobronchial NSCLC which obstructs a bronchus and which is refractory to conventional therapy.

PATIENT ELIGIBILITY

1) Patients must have histologic proof of non-small cell lung cancer. Patients must be either unresectable, unable to receive primary external beam radiation therapy, or have failed primary external beam radiation therapy.
2) Patients must have an endobronchial tumor accessible by the bronchoscope. There must be some clinical evidence of bronchial obstruction.
3) All patients must have a life expectancy of at least 12 weeks and must have a performance status of ≤ 2 (Zubrod scale, Appendix B).
4) All patients must sign an informed consent indicating that they are aware of the investigational nature of this study in keeping with the policies of the hospital. The only acceptable form is the one attached at the end of this protocol.
5) A tumor biopsy must show either a K-ras mutation or a p53 mutation by single-strand conformation analysis.

TREATMENT PLAN

1) Patients will undergo bronchoscopy to assess the degree of obstruction. As much gross tumor as possible will be resected endoscopically. Patients may also have had brachytherapy as a tumor reduction modality.
2) Patients will undergo bronchoscopy under topical or general anesthesia. A Stifcor™ transbronchial aspiration needle (21g) will be passed through the biopsy channel of the bronchoscope. Tumor will be debulked endoscopically. The residual tumor site will be injected with 10^7 CFU/ml of the appropriate retroviral supernatant. The volume will be no greater than 10 ml. Injections will be circumferential and will be intratumor and submucosal. The AS-K-*ras* supernatant will be used for K-*ras* mutations and the *p53* supernatant will be used for *p53* mutations. The injections will be repeated daily for five consecutive days. The treatment will be repeated monthly.

PRETREATMENT EVALUATION

Pretreatment evaluation will consist of a complete history and physical including performance status, weight loss, description of previous and current malignant and non-malignant diseases and their treatment, and residual toxicities; location and size of the endobronchial lesion; chest x-ray, and laboratory studies including: quantitative immunoglobulins; a CBC with differential and platelet count; SMA-12 and electrolytes, including creatinine, bilirubin, SGPT, alkaline phosphatase, and urinalysis.

Prior to each course of therapy, the following clinical data will be ascertained and recorded:

1. CBC, platelet count, PT, PTT, SMA-12, electrolytes, and a chest x-ray.
2. Measurement and bronchoscopic photograph of tumor.
3. All relevant information regarding drug dosage, tumor response, laboratory examinations, and treatment-related toxicities.

The primary endpoint of the study will be regrowth of the tumor. The effect of therapy in this group of patients will also be measured by determining length of patient survival, length of time the affected lobe of the lung remains aerated, and reduction in measurable endobronchial tumor. A maximum of 14 patients will be recruited in this study.